Role of and indications for bypass surgery after carotid Occlusion Surgery Study (COSS)?

Esposito, Giuseppe ; Amin-Hanjani, Sepideh ; Regli, Luca

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The role of and indications for bypass surgery after COSS?

Giuseppe Esposito , MD, PhD

Department of Neurosurgery, University Hospital Zurich, University of Zurich

Frauenklinikstrasse 10 - CH-8091 Zürich, Switzerland

E-mail: giuseppe.esposito@usz.ch

Sepideh Amin-Hanjani, MD

Department of Neurosurgery, University of Illinois at Chicago

Neuropsychiatric Institute, Rm 451N, 912 S Wood St, M/C 799, Chicago, IL 60612, USA

E-mail: hanjani@uic.edu

Luca Regli, MD

Department of Neurosurgery, University Hospital Zurich, University of Zurich

Frauenklinikstrasse 10 - CH-8091 Zürich, Switzerland

E-mail: luca.regli@usz.ch

Corresponding author:

Luca Regli, MD

Department of Neurosurgery, University Hospital Zurich, University of Zurich, Switzerland Frauenklinikstrasse 10 - CH-8091 Zürich. Tel: +41-44-2552660 - Fax: +41-44-2554387 E-mail: luca.regli@usz.ch

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INTRODUCTION

Bypass surgery falls into two distinct categories: "flow-augmentation" and "flow-preservation". Flow-augmentation aims to restore flow to hypoperfused brain territories in patients with steno-occlusive diseases.[1] Flow-preservation aims to replace the blood flow provided by a major intracranial vessel, the sacrifice of which is necessary for treating an underlying disease, such as an aneurysm or a tumor.[2, 3]

Flow augmentation bypass has been critically studied in randomized clinical trials (RCTs),[4-6] most recently the Carotid Occlusion Surgery Study (COSS)[5] and the Japanese Adult Moyamoya (JAM) trial[6], whereas flow preservation bypass remains a niche procedure due to **its rare indication**[2, 3, 7, 8].

In this review, we aim both to critically summarize the current state of knowledge on the role of cerebral bypass surgery since the publication of COSS and to present possible future directions for surgical cerebral revascularization.

Bypass technique

Beyond the underlying disease and the consequent aim that defines the two categories of bypass (see above), several other criteria are used to classify bypass constructs. A well-known classification is the distinction into "direct vs. indirect" revascularization procedures or the combination of both.[9, 10] Direct bypasses consist of direct anastomosis between a donor artery and an intracranial recipient artery. A direct bypass has the advantage of instantly delivering blood flow to the brain.[1, 2, 7] Indirect techniques rely on the overlay of vascularized tissue (i.e.: muscle, dura, pericranium, omentum) onto the cerebral cortex in order to promote neoangiogenesis over time and achieve a delayed revascularization. [10, 11] Combined procedures consist of the "combination" of direct and indirect techniques in the same surgical session[10].

According to the origin of the donor artery, direct bypass is further categorized into "extra-to-intracranial (EC-IC) vs. intracranial-to-intracranial (IC-IC)". Furthermore, the donor and the recipient artery can be anastomosed "with vs. without graft interposition", depending on the interposition or not of a vascular conduit (i.e.: arterial or venous graft).[3, 7] Traditionally the bypass will be named according to the donor and the recipient vessels (i.e.: superficial temporal artery to middle cerebral artery - STA-MCA - bypass).[2]

The type (end-to-side, end-to-end, side-to-side) and the number of microanastomosis also vary depending on patient specific indications and angioanatomy.[2] The surgeon can further use the conventional "occlusive" microanastomosis technique or apply a "non-occlusive" technique (e.g.: Excimer Laser-Assisted Non-occlusive Anastomosis – ELANA – technique). [12]

Direct bypass procedures can be also categorized according to the amount of flow (the capacity) provided by the construct: low (<50 ml/min) vs. intermediate (50-100 ml/min) vs. high-capacity bypass (>100ml/min).[3] Figures 1-2 schematize the most commonly used bypass procedures.

The choice of the ideal bypass depends on several factors, the most important of which are the indication and the aim for the bypass, as well as the match between the flow demand of the revascularized brain territory and the flow capacity of the bypass. Indications will be discussed in the next sections.

INDICATIONS FOR CEREBRAL BYPASS

FLOW PRESERVATION

Complex intracranial aneurysms

Complex intracranial aneurysms (cIA) are not always amenable to selective clipping, coiling or

other endovascular procedures. Treatment of such lesions may require “trapping”, i.e. exclusion of the aneurysm with sacrifice of the artery bearing the aneurysm.[2, 7] Since the goal of any aneurysm treatment is both aneurysm exclusion and preservation of blood flow to the brain, flow-preservation bypass strategies represent an essential treatment option, in order to divert blood flow to downstream vascular territories (territory supplied by the occluded vessel/s).[2, 3, 7, 12] For a detailed description of types and indication of trapping strategies, we refer to the pertinent literature. [2, 3, 7, 8, 13, 14]

Matching the bypass flow to the demand of the brain territory perfused by the sacrificed artery is the key-element of decision-making when performing a flow-preservation bypass.[2, 7, 8] Preoperative and intraoperative quantitative flow measurements are necessary to predict the flow and to confirm that the capacity of the bypass matches the flow demand of the vascular territory.[2, 7, 8]

No RCTs to test the value of bypass surgery for treating cIAs have been performed. Due to the rarity and variety of cIAs, it has not been feasible to perform large-scale trials. **Furthermore the evolution of endovascular treatments for cIAs tends to decrease the indication for flow-preservation bypass.[15]** Nevertheless, bypass is established by a multitude of case series which document the usefulness of revascularization and demonstrate that bypass surgery plays an important role for managing cIAs.[2, 3, 8, 13, 14]

Cerebral tumors involving the proximal vasculature

Benign skull base tumors tend more to encase than invade major arteries. However, in case of previous surgery or irradiation, tumors can be densely adherent to the arterial wall. Malignant skull base tumors are more prone to invade major arteries. Radical tumor removal can therefore be impossible in some skull base tumors without sacrificing a major artery.[16]

The risk-benefit ratio for complete resection combined with a bypass versus partial resection has evolved in favor of partial resection and adjuvant radiotherapy or chemotherapy.[16, 17] Thus flow-

preservation bypass for skull base tumors has declined in frequency during the last decades. Bypass surgery is currently performed only in very selected and rare cases, in which it is of importance to consider whether the benefit of radical resection plus arterial sacrifice and bypass improves survival with good quality of life, and outweighs the risks. [3, 16-18]

FLOW AUGMENTATION

Moyamoya vasculopathy

Moyamoya vasculopathy is a rare steno-occlusive condition characterized by idiopathic intimal thickening of the internal carotid artery (ICA) and its proximal branches.[9] Moyamoya progressively compromises cerebral perfusion and hemodynamics, predominantly in the middle cerebral artery (MCA) territories and in the frontal areas, and patients develop compensatory collateral vascular networks.[1, 9]

Symptoms are brain ischemia (stroke, TIAs) or brain hemorrhage, due to either the insufficiency or the rupture respectively of the compensatory collateral vessels under hemodynamic stress..[1, 9]

There is currently no medical treatment that can halt progression or reverse the vasculopathy.[9, 10] Surgical revascularization is considered the only effective treatment modality.[1, 6, 10]

Although the value of bypass surgery for prevention of stroke and of cognitive deterioration in Moyamoya patients has not been studied with RCTs, all observational studies indicate the benefit of cerebral revascularization.[10, 19, 20] The literature consistently documents: 1) unfavorable annual ischemic stroke rate in untreated patients (up to 13.3%)[21]; 2) high rate of disease progression with subsequent symptoms occurrence in the non surgically treated hemispheres[22]; 3) favorable result of revascularization both in children and adults[10]. Therefore it seems unlikely that RCTs will be performed to test the efficacy of revascularization surgery for prevention of stroke recurrence and

of cognitive deterioration.[10, 19, 20]

Surgery is recommended for children and adults with ischemic symptoms and compromised hemodynamics.[1, 10, 19, 20, 23] Careful observation is justified in asymptomatic patients with normal cerebral hemodynamics.[10] Figure 3 describes the stages of cerebral hemodynamic impairment.

There is no consensus on what type of revascularization surgery should be performed. Direct, indirect and combined bypass procedures are used for treating Moyamoya.[9, 10] The choice of technique remains debated in the literature, both in adults and in children.[10, 11] The most commonly used direct revascularization procedure is the STA–MCA bypass (Figure 2, left panel). Other extracranial donor vessels can also be used (for instance the occipital or the posterior auricular artery). [1, 9]

Several indirect techniques have been proposed using the overlay of vascularized tissue (periosteum, muscle, dura) onto the cerebral cortex to promote neoangiogenesis over time.[1, 10] (Figure 2, right panel – Supplemental Material). Combined revascularization procedures combining direct and indirect bypass, provide the advantages of both techniques, but at the risk of a somewhat more complex procedure.[1, 10]

Adult patients are generally treated by means of direct bypass techniques (typically STA-MCA bypass), in comparison to children for whom indirect or combined revascularization strategies are preferred [9, 10]

Although most techniques aim to revascularize the MCA territory, augmentation of cerebral blood flow (CBF) of the frontal areas is of importance especially in the pediatric population. Bifrontal hypoperfusion plays an deleterious role in intellectual development and cognitive performance, and in lower extremity and sphincter function.[24, 25] Therefore, it is important to consider timely revascularization of the frontal areas, to prevent neurocognitive decline.[24, 25]. Besides the direct STA to anterior cerebral artery (STA-ACA) bypass[26], indirect and combined bypass techniques have been proposed for bifrontal reinforcement of blood supply[1].

The role of surgical treatment in Moyamoya presenting with intracerebral bleeding has been recently demonstrated with the "*Japanese Adult Moyamoya (JAM) Trial"*,[6] the first prospective RCT focused on Moyamoya disease (MMD). Eighty adult patients (between 16 and 65 years) with hemorrhagic MMD were enrolled and randomized, 42 to the surgical and 38 to the non-surgical group. In the surgical group patients underwent bilateral direct bypass. Indirect bypass alone was prohibited in the study protocol, as indirect revascularization believed to be associated with insufficient neoangiogenesis in adult patients.[23] Although statistically marginal, the JAM Trial revealed that direct bypass surgery for adult patients with hemorrhagic-MMD reduces the re-bleeding rate and improves the patient's prognosis during the 5 years after enrollment.[6] This trial showed that improvement of the hemodynamic state of the revascularized hemisphere reduces the hemodynamic overload of the rupture-prone fragile moyamoya collateral vessels.[6] Recurrent bleeding can however take place >10 years after the initial attack.[27] Therefore, these patients warrant longer-term observation, and the JAM Trial Executive and Steering Committee has already decided to continue patients' follow-up, and report the 10-year results when available.[6]

All institutions participating in the trial had vast experience with treatment of patients with MMD. Only registered surgeons were allowed to perform the operations. The rate of perioperative complications, including transient events, was 9.5%. No permanent severe disability was reported.[6]

Symptomatic cerebrovascular atherosclerotic steno-occlusive disease.

Cerebrovascular atherosclerotic occlusion of one or more extracranial brain feeding arteries or intracranial major arteries (e.g.: ICA, MCA) can lead to ischemic symptoms.[4, 5]

Indirect cerebral revascularization methods are felt to be largely ineffective for non-moyamoya vasculopathy[28, 29], due to the presumed absence of the angiogenic milieu associated with MMD, although small case series have suggested some limited success with indirect strategies.[30] Currently,

a RCT, the *"EDAS (Surgical) Revascularization in patients with Symptomatic Intracranial Arterial Stenosis (ERSIAS)"* is underway in USA which may provide some insights into the role of indirect bypass for atherosclerotic disease (ClinicalTrials.gov NCT01819597) (EDAS: encephalo-duro-arterio-synangiosis). Beyond this, for atherosclerotic occlusions, the primary focus has been on examining the role of direct cerebral bypass. [28, 31]

The *"EC-IC Bypass Trial"* published in 1985 was the first prospective RCT aimed at investigating whether EC-IC bypass was superior to best medical therapy alone for stroke prevention.[4] The study was conducted in 1377 symptomatic patients with: 1) one or more TIAs or minor ischemic strokes within 3 months of enrollment, and one of the following: 2) stenosis or occlusion of the MCA proximal trunk, 3) stenosis of the ICA above the C-2 vertebral body (inaccessible to carotid endarterectomy), or 3) atherosclerotic ICA occlusion.[4] The average follow-up duration was 55.8 months. Bypass patency rate was excellent (96%). However, the trial showed no significant difference between the two randomized groups: 29% of medically treated patients experienced one or more strokes compared with 31% in the surgical group. No significant difference in the incidence of fatal and nonfatal ischemic strokes was reported.[4, 28] This study was fiercely debated.[32] One of the primary criticisms related to the lack of hemodynamic criteria used to identify and select those high-risk patients who might benefit most from bypass [28, 33, 34]

A Cochrane review[31] published in 2010 reported the results of 21 trials (two RCTs and 19 non-random studies) for total of 2591 patients with symptomatic carotid occlusion. This review showed bypass was neither better nor worse than medical care alone. [31] Again most of the analyzed studies lacked hemodynamic criteria for patients' inclusion. [28]

Since the original EC-IC Bypass Trial, methods and criteria for quantification and assessment of cerebral hemodynamic impairment were validated (Figure 3). The *"St Louis Carotid Occlusion Study"(STLCOS)*[33] was a prospective study showing that symptomatic patients with carotid occlusion and presenting stage-II hemodynamic impairment (increased oxygen-extraction-fraction with positron emission tomography-OEF-PET) were at significantly increased risk of ipsilateral

stroke at 2 years compared to patients without stage-II hemodynamic impairment (26.5% vs 5.3%).[28, 33] During the same period, several other studies demonstrated that in stage-II patients bypass was able to improve or even normalize the hemispheric OEF-ratios post-operatively.[28] Therefore all the conditions were present to justify a new RCT to test the hypothesis that EC-IC bypass surgery would benefit patients with recently symptomatic atherosclerotic carotid occlusion when selected according to strict validated hemodynamic criteria.[28, 33, 35 36]

The "*Carotid Occlusion Surgery Study (COSS)"* [5] was a prospective, multi-center RCT designed to assess whether STA-MCA bypass (plus best medical therapy) was superior to best medical therapy alone in stroke prevention in patients with: 1) complete ICA occlusion; 2) TIA or ischemic stroke in the hemispheric territory of an occluded ICA in the preceding 120 days.[5] The participants underwent PET at COSS-approved sites. Patients' neurological deficits were required to be stable for 72 hours prior to the performance of PET. Those presenting with ipsilateral-to-contralateral hemispheric OEF-ratios >1.13 (derived from retrospective STLCOS subgroups analysis identifying a very high-risk patient cohort) were selected and randomized.[28, 32, 33, 35] The study was prematurely stopped in June 2010 by the Data Safety Monitoring Board after enrollment of 195 randomly assigned patients because of interim futility: 97 patients were randomized to the surgical group and 98 to the medical group.[32, 34] The 2-year rates for ipsilateral stroke were 21% for the surgical group vs. 22.7% for the medical group (p=0.78). Perioperative (within 30 days of surgery) ipsilateral stroke rates were 14.4% in the surgical group and 2.0% in the medical group, a significant difference of 12.4%.[32, 34] STA-MCA bypass surgery was shown to provide no clinical benefit over medical therapy.[5] Notably, the medical therapy cohort fared better overall than the historical control group. [37]

Subsequently published COSS-data showed: 1) high rates of bypass patency (98% and 96%, at 30-day and at last follow-up respectively); 2) bypass surgery improved, but did not normalize, cerebral hemodynamics (OEF-PET analysis 30- to 60-day follow-up); 3) the OEF-improvement greatly reduced the risk of subsequent stroke in these patients; 4) the surgical group had much lower rates

of recurrent ipsilateral ischemic stroke after post-op day-2 as compared with the medical group (9% vs 22.7%); 5) no patient characteristics or intraoperative variables were able to predict the occurrence of ipsilateral, periprocedural ischemic stroke.[38]

Further reports from COSS investigators studied the mechanisms of perioperative ischemic stroke. In patients (n=14) who developed ipsilateral perioperative ischemic stroke, 14% of stroke mechanisms (2 patients) were found to be bypass related (ischemic infarct in the territory of the recipient artery, likely related to technical performance of the anastomosis) and 86% (12 patients) were non-bypass related mechanisms (ischemic infarct attributable to embolism, hypoperfusion,etc).[39] These perioperative events were proposed to be likely attributable to the fragility of individuals with symptomatic carotid occlusion and severely impaired hemodynamics, rather than to poor surgical techniques. [28, 39]

COSS faced nourished criticism following its publication in 2011, focused on clinical eligibility criteria, PET-eligibility criteria, selection of surgeons, duration of follow-up, power and end-points.[32, 34] These were addressed by Powers et al. in subsequent commentaries.[36, 40] In particular, it has been argued that patients with symptom recurrence despite medical therapy after a carotid occlusion represent a subgroup of patients that could ultimately benefit from surgery. In fact COSS only required patients to have a single ischemic event to be eligible for the trial, whereby the single ischemic event at the time of carotid occlusion might represent a single embolic event.[32] However Powers pointed out that 1) "neither earlier enrollment nor recurrent ischemia identified patients at high risk of recurrent stroke in COSS"; 2) "these findings are consistent with data from the EC-IC Bypass Trial in which neither the subgroup with earlier surgery nor the subgroup with recurrent symptoms showed benefit from surgery"; 3) "similarly in STLCOS, neither recurrent symptoms nor time from qualifying event to enrollment were associated with subsequent stroke occurrence."[36] Furthermore, it has been speculated that the continuation of the event rate observed during the first 2 years would have been responsible of a significant difference if the study had been continued for 5 years. As stated by COSS investigators, such an assumption would be inconsistent with data from

other trials of medically treated symptomatic large artery atherosclerosis that show a major decrease in stroke rate after 2 years. For instance in the EC-IC Bypass Trial, the stroke rate at 2 years was 20%, but at 4 years the stroke rate had only increased by an additional 6%.[4] A 2% to 3% / year-rate of stroke in the nonsurgical group of COSS for an additional 3 years would not result in a statistically significant benefit for surgery, even if no additional strokes occurred in the surgical group. The COSS final results, even with early termination for futility, excluded with greater than 95% confidence a benefit for surgery.[28, 39]

Not-addressed criticisms remain: the lack of selection-requirements for specialized neuroanesthesia, dedicated neurointensive care, specialized nursing. Similarly, no recommendations were established for a perioperative management protocol.[32] Nevertheless the practicality of performing such large-scale studies has also been debated, considering the high number of patients and high cost needed to demonstrate the superiority of one treatment on the other.[32]

The *"Randomized Evaluation of Carotid Occlusion and Neurocognition" (RECON) Trial*[41] is an ancillary study of the COSS. Given the evidence from prior studies that cerebral hemodynamic is a determinant of cognitive function, RECON aimed to test if bypass could improve or preserve neurocognition at 2 years in COSS patients, in comparison with best medical therapy alone.[41] Eighty-nine patients were enrolled; 41 had increased OEF and were randomized. Two died, 2 were lost to follow-up, and 2 refused re-testing. Of the 35 remaining, 6 had ipsilateral stroke or death, leaving only 13 surgical and 16 medical patients. Due to the early termination of the parent study (COSS) RECON was not able to complete enrollment, although 2-year follow-up for the already randomized individuals was completed. Controlling for age, education and depression, RECON showed that for patients with symptomatic carotid occlusion and stage-II hemodynamic impairment bypass provides no benefit on neurocognition after 2 years, compared with medical therapy alone.[41] The small numbers however limit the power of this study.[41]

The *"Japanese EC-IC Bypass Trial (JET)"* was a multicenter RCT designed to assess whether STA-MCA bypass (plus best medical therapy) is superior to best medical therapy alone in reducing

subsequent ischemic events in patients with recently symptomatic hemodynamic (at least stage-I on Single-photon emission computed tomography-SPECT; figure 3) cerebral ischemia from chronic ICA or MCA occlusion. [42-44] 196 patients were enrolled and randomized 50:50. [28, 42, 44] An interim analysis with a mean follow-up of 15 months reported a statistically significant reduction of major stroke and death (primary outcome) in the surgical arm (5.1%) as compared with the medical one (14.3%).[43, 44] The published Kaplan-Meier curve showes however no end points within the first month in the surgical group: it is not mentioned if the results include the morbidity and mortality rate of the first post-operative month.[28 43, 44] As commented by Powers et al. (2011), "it seems unlikely that this rate was 0 % given that it was 12% in the original EC-IC Bypass Trial and 15 % in the COSS".[5] JET final results have not yet been published in a peer-reviewed, English written journal.[43, 44] Therefore, it is difficult to include JET study results into the general evidence base regarding bypass in atherosclerotic disease.

Currently, a large-scale multicenter RCT, the *"Carotid and Middle Cerebral Artery Occlusion Surgery Study" (CMOSS)*, is underway in China which may provide further insights into the role of bypass for atherosclerotic disease (ClinicalTrials.gov NCT01758614).

Considerations in patients with atherosclerotic steno-occlusive disorder

Level I evidence from both the EC-IC Bypass Trial and COSS indicates that bypass does not have proven benefit in patients with recently symptomatic carotid artery occlusion with or without stage-II hemodynamic failure.[4, 5, 28] RECON furthermore failed to demonstrate that for these same patients with stage-II hemodynamic failure, bypass improves cognitive function after 2 years.[28, 41]

Advances in medical management and lifestyle modification appear to have reduced stroke risk in these patients and made the ''proof of benefit'' of surgery more difficult to achieve.[34] The SAMMPRIS trial, for example, showed that an aggressive strategy, including low-density

lipoprotein target below 70 mg/dL, as well as vigilant targeting of blood pressure, diabetes mellitus, smoking, excessive weight, and inactivity, resulted in substantially lower stroke rates in patients with intracranial stenosis.[45] Nonetheless, although best medical therapy is more effective than in the past, it is still not curative and many patients with severe hemodynamic insufficiency fare poorly. [32]

The results of these trials significantly narrow the indications for flow-augmentation bypass for atherosclerotic steno-occlusive cerebrovascular disease with chronic hemodynamic insufficiency. However, rather than a blanket rejection of bypass surgery for all patients with atherosclerotic cerebrovascular disorders, we want to address two challenging questions in this review: 1) are there methods to reduce perioperative complications in the very early postoperative period? 2) are there methods to identify select subgroups of patients that could benefit from bypass surgery?

With regard to the first question, a significant reduction of perioperative ischemic complications could change the current statement of "no benefit from bypass". [28] The COSS eligible patient might still benefit from flow-augmentation bypass if perioperative morbidity can be sufficiently lowered, much lower than reported in COSS and EC-IC bypass trial.[28] Low perioperative morbidity is therefore a key development to aim for.[43] COSS-patients have been considered fragile and at high risk for perioperative ischemic events. Although surgeons underwent certification for participating into COSS, no selection requirements were established for specialized neuroanesthesia, dedicated neurointensive care, and specialized nursing. Similarly, no recommendations were established for a perioperative management protocol.[32, 43] Despite lower perioperative complication rates have been reported in several cases series[43, 46], the most reliable perioperative morbidity rates are considered to be from RCTs. Indeed, as cited by Powers [36], "self-reported case series have been shown to consistently underreport operative complications in comparison with independent adjudication"[47] and "observational studies with historical controls from case series have been repeatedly shown to overestimate benefit and underestimate risk in comparison with RCTs".[36] Due to the similarity of perioperative morbidities in the EC-IC bypass trial (12%) [4] and COSS (15)[5], it will need a thorough analysis of the comprehensive perioperative management - surgical, anesthesiological and medical -

of these fragile patients in order to prove that the reduction of perioperative complications is possible. A RCT, however, is not the only mechanism to establish improvements in perioperative risk. Prospective adjudicated observational data, as can be achieved with well-administered and audited registries, can serve to provide such data. The Society of Thoracic Surgeons (STS) National Database represents an example of prospective registry data on outcomes.

Finally, technical innovation such as the "systematic" use of minicraniotomy (2-2.5 cm) may represent an opportunity to lower the peri-operative complications rate.[48]

The second question aims to identify subgroups of patients that would benefit from bypass.[37] There are distinct subgroups of patients, for whom COSS was not specifically designed: patients with chronic retinal ischemia resulting in progressive visual loss and patients presenting with ongoing hemodynamic symptoms despite optimal medical therapy.[28, 36] These are patients who develop ischemic symptoms with postural changes or blood pressure variation (for instance patients with debilitating orthostatic hypoperfusion syndrome or limb-shaking TIAs).[28] Furthermore, there are patients with symptomatic carotid occlusion and particularly marked hemodynamic impairment (more severe than the OEF ratio >1.13 used in COSS), who may have a significant risk for subsequent stroke.[28, 36] In this context, particular attention should be given to patients harboring multiple extracranial arterial occlusions, not amenable to carotid endarterectomy or stenting, who are symptomatic despite best medical therapy. All these patient subgroups above have hemodynamic conditions indicating exhausted brain vascular reserve capacity with symptomatic oligoemia exacerbated by any hemodynamic challenge. These patients were included in neither trial and represent possible bypass candidates, if surgery can be performed with low enough morbidity. The eventual benefit of bypass surgery over medical therapy in these individuals will most likely not be testable in RCTs.

Finally, a different subgroup that may benefit from bypass are patients suffering acute stroke with brain tissue at risk of infraction due to persistent oligoemia in the acute phase (=penumbra), despite optimal medical and interventional management. In patients with acute or evolving stroke, outcome

is known to be dependent on the urgent reestablishment of cerebral perfusion.[49] Several different reperfusion methods are available: intravenous thrombolysis, intra-arterial thrombolysis or mechanical thrombectomy, carotid endarterectomy, angioplasty/stenting, surgical embolectomy, and EC-IC bypass.[50] Level I evidence now exists for endovascular interventions[51-53] in an emergency setting. Only few descriptive case series exist describing the role of urgent EC-IC bypass in treating patients with acute and progressive ischemic symptoms despite optimal medical therapy due to acute atherosclerotic steno-occlusive event; these report good results in term of patients' outcome[50, 54, 55]. These case series all have a retrospective design and are therefore vulnerable to selection bias. Furthermore they have been published before the recent RCTs reinforcing the role of endovascular therapy for stroke.[51-53] On one hand one may state that the efficacy and safety of emergent EC-IC bypass would need to be proven by studies using adequate analytical multicenter designs. On the other hand, given the rarity of the bypass procedures performed worldwide nowadays, it is of importance to assure that these patients are referred to specialized neurovascular centers, with sufficient expertise. This stands against the call for RCTs on emergent bypass surgery as a treatment option for acute revascularization.

We however hypothesize that there is a very small number of patients suffering from acute stroke with persistent penumbra that cannot benefit from other acute revascularization interventions, and may benefit from emergent EC-IC bypass, if the procedure can be performed with low enough morbidity. [55] One of the key-elements is to define the method to select these patients suffering acute stroke and who have persistent "ischemic penumbra" with limited core infarct, indicating ischemic tissue still viable and salvageable if local perfusion is efficiently restored. [54] The concept of 'mismatch' is an attempt to define ischemic penumbra by neuroimaging[49, 53] A detailed analysis and definition of the mismatch concept is beyond the scope of this review and we refer to the relative literature.[49 53] Among individuals suffering acute or evolving stroke, patients who could benefit from bypass surgery might be the ones presenting with the 3 following criteria: 1) acute stroke or

stroke in progress (fluctuating or worsening symptoms) despite maximal applicable medical and interventional treatment; 2) major cerebral artery occlusion, with documented region of penumbra and 3) only a small area of infarction (to avoid hemorrhagic conversion of an acute infarction)[49, 53, 54]. Without an adequately designed analytical study to test this hypothesis, this remains an unproven but intriguing potential indication for revascularization using bypass.

CONCLUSIONS

We essentially distinguish two types of bypass, according to function: flow-preservation and flow-augmentation bypass. Flow-preservation bypass surgery plays an important role in the management of complex intracranial aneurysm not amenable to selective clipping or endovascular procedures, when vessel sacrifice is required for definitive treatment. Matching the bypass flow capacity to the flow demand of the territory that needs to be revascularized is the key-element of flow-preservation bypass. Technical variations in the bypass construct allow the surgeon to customize the bypass to the patient's need. The bypass will always be a direct bypass, in order to deliver the flow instantly to the involved territory.

Flow-augmentation bypass is the only effective treatment modality for symptomatic Moyamoya patients with hemodynamic insufficiency. Revascularization has been shown to decrease both ischemic and hemorrhagic stroke rates as well as neurocognitive decline. Revascularization surgery for Moyamoya comprises both direct and indirect techniques depending on patient age, the vascular regions to revascularize and the individual angioanatomy. Not infrequently the surgeon will decide to perform a combination of direct and indirect revascularization techniques.

COSS and RECON trials showed no benefit of bypass over medical therapy for patients with atherosclerotic ICA occlusion with severe hemodynamic impairment due to the increased perioperative morbidity. These results narrow the indications for flow-augmentation EC-IC bypass

in the setting of ischemic cerebrovascular disease.

The following observations deserve, however, attention for future developments. COSS results showed a reduction in subsequent event rates in the bypass group, despite the failure to show an overall benefit from surgery. These data confirm the basic concept of EC-IC revascularization and indicate that if perioperative complications could be lowered, benefit is likely.

Patients with severe steno-occlusive disease continue to have significant event rates, despite medical therapy having become more effective. Further studies and improvement in perioperative management may benefit these brittle patients.

Furthermore, COSS was not designed to study two particular categories of patients: (1) patients presenting with ongoing hemodynamic symptoms (postural or with blood pressure variations) resistant to best medical treatment; (2) patients suffering acute stroke with evidence of persistent oligemic brain tissue at risk of infarction (penumbra) despite optimal medical and interventional management. The general concept of non-surgical brain revascularization for penumbra salvation is proven in the clinical setting, through endovascular recanalization trials, and could be extended to the concept of urgent bypass in highly select patients. The benefit of interventions has to be weighed against its risks, and further prospective studies are necessary to prove the eventual benefit of bypass in selected patients with atherosclerotic steno-occlusive disorders.

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FIGURE LEGENDS

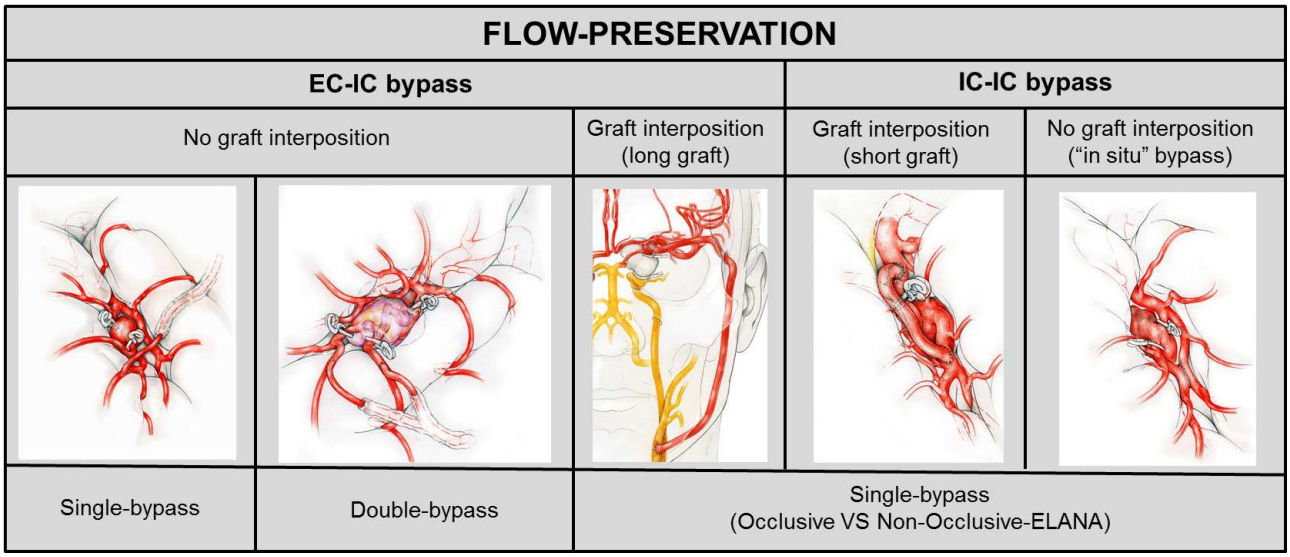

Figure-1.

Representation of flow-preservation bypasses.

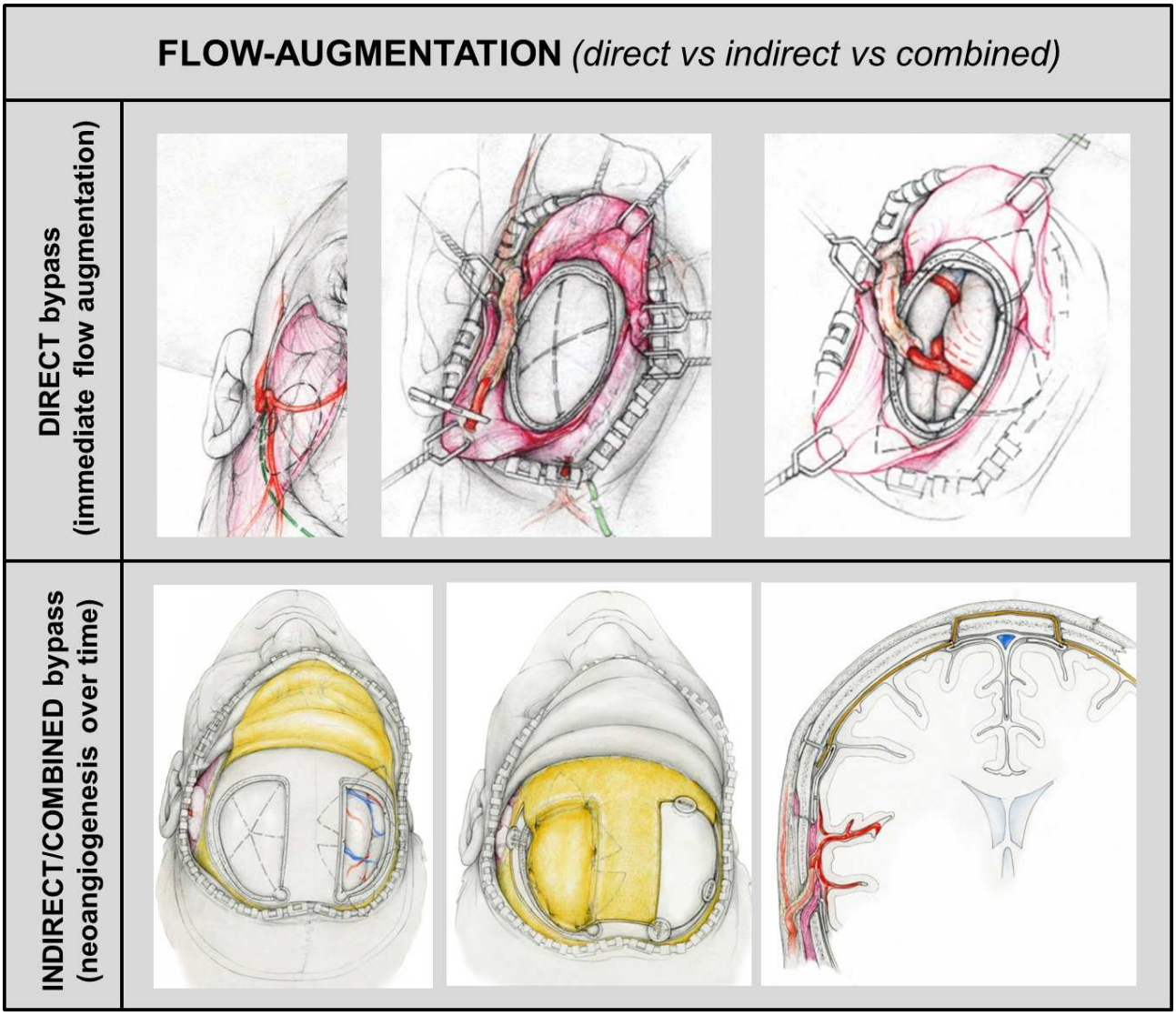

Figure-2.

Flow-augmentation strategies. Left-panel: direct (STA-MCA) bypass. Right-panel: combined revascularization consisting of unilateral STA-MCA bypass plus encephalo-duro-myo-synangiosis and bifrontal encephalo-duro-periosteal-synangiosis. (*Modified from Esposito G, Kronenburg A, Fierstra J et al, 2015*)[1]

THE 3 STAGES OF HEMODYNAMIC IMPAIRMENT

Stage	Pathophysiology	Flow	Metabolism	Hemodynamics	
		CBF	CMR	CVR*	OEF**
I	Drop of CPP (lack of collaterals) ↓ Cerebral vasodilatation	*Normal*	*Normal*	*Reduced*	*Normal*
II	Further drop of CPP ↓ Cerebral vasodilation exhausted ↓ OEF increase	*Reduced*	*Normal*	*Exhausted*	*Increased*
III	Further drop of CPP ↓ CVR and OEF exhausted ↓ Ischemia	*Reduced*	*Reduced*	*Exhausted*	*Exhausted*

*: CVR describes how far cerebral perfusion can increase from a baseline value after stimulation. Impaired CVR is defined as a reduced or absent CBF after vasodilatory stimulus. CVR is measurable via transcranial Doppler, Xenon-CT, SPECT, PET, MRI by acquisition of an initial CBF measurement at rest and a subsequent CBF measurement after a vasodilatory stimulus (i.e.: acetazolamide or hypercapnia).

**: OEF is the percent of the oxygen removed from the blood by tissue. OEF can be calculated via OEF-PET.

Abbreviations: Cerebral blood flow (CBF); cerebral metabolic rate (CMR); Cerebral perfusion pressure (CPP); cerebrovascular reserve (CVR); computed tomography (CT); Magnetic Resonance Imaging (MRI); oxygen extraction fraction (OEF); Positron emission tomography (PET); Single-photon emission computed tomography (SPECT).

Figure-3.

The pathophysiology and the 3 stages of hemodynamic impairment.

Indirect cerebral revascularization procedures for moyamoya vasculopathies

INDIRECT BYPASSES
Encephalo-myo-synangiosis (EMS) [1]
Encephalo-duro-myo-synangiosis (EDMS) [1]
Encephalo-arterio-synangiosis (EAS)[2]
Encephalo-myo-arterio-synangiosis (EMAS)[3]
Encephalo-duro-arterio-myo-synangiosis (EDAMS)[4]
Encephalo-duro-arterio-synangiosis (EDAS)[5]
Encephalo-duro-periosteal-synangiosis (EDPS)[1]
Multiple burr-holes[6]
Omental transplantation[7]

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